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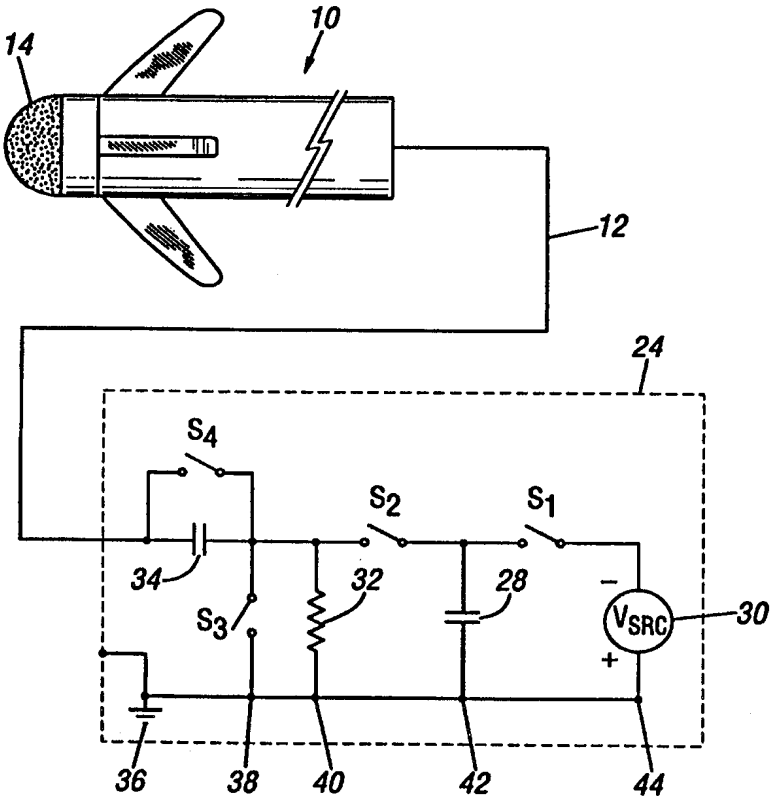
(57) Abstract

The invention relates to implantable electrodes (10). More particularly, it relates to implantable cardiac electrodes. It more specially relates to such electrodes (10) capable of controllably–releasing a drug such as a steroid at the electrode in the target tissue (26). The controlled release of the drug is achieved using an iontophoretic or iontokinetic process, and does not require additional conduits for the drug nor additional mechanical components over those typically found in such stimulation leads.



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Description

Controllable Drug Injection Electrode

Technical Field

The invention relates to implantable electrodes. More particularly, it relates to implantable cardiac electrodes. It more specifically relates to such electrodes capable of controllably-releasing a drug, such as a steroid, at the site of implantation of the electrode in the target tissue. The controlled release of the drug is achieved using a iontophoretic or iontokinetic process.

Background Art

Stimulation electrodes must overcome the stimulation threshold in order to deliver an effective electrical stimulus to a target tissue in which the electrode is implanted. In cardiac pacing, the stimulation threshold is a measure of the amount of energy required in order for a pulse to initiate and maintain regular, rhythmic cardiac contractions. When such leads are initially implanted into a target tissue, the stimulation threshold is typically low. Immediately after implantation, however, the stimulation threshold begins to rise, and may do so for a number of weeks until the physiological environment at the site of insertion of the electrode stabilizes. It is generally believed that the rise in the stimulation threshold results from increased spacing or electrical resistance of the tissue between the electrode and the target tissue, and that such increased spacing and resistance is a result of the inflammatory response and subsequent development of fibrous capsule materials around the electrode tip.

Generally upon implantation, a clot forms in about 1-2 days around the tip of the lead where it is affixed to the myocardium. In the damaged portion of the myocardium thereafter, ranging from about 36 hours up to 3-4 weeks, fibrotic activity is seen to occur. During this time, a peak in inflammation in the wound occurs about 3-6 days post implantation. This series of wound-clot-inflammation-fibrosis-stabilization can recur if additional trauma at the lead insertion site occurs, such as by movement or shifting of the lead. Thus, there are a number of windows in the implantation and maintenance of a stimulation lead which can benefit from techniques designed to lessen the effects of clotting, inflammation and fibrosis.

It is known that stimulation threshold-reducing drugs can be diffused into target tissue (e.g., myocardium) in order to cause the reduction of inflammation, thrombosis or fibrosis. For that reason, efforts have been made to devise drug-delivery systems to be used in combination with stimulation of certain tissues, particularly the heart.

Drug-eluting stimulation leads have been described previously. *See. e.g.*, U.S. Patent No.

4,506,680 (Stokes). Such implantable devices rely exclusively on a passive drug-elution mechanism which cannot be controlled by the implanted device. Elution is a process in which an adsorbent is washed out or otherwise removed by means of a solvent. *See also*; U.S. Patent Nos. 4,577,642 (Stokes), 4,711,251 (Stokes), 4,819,661 (Heil, Jr.), 4,819,662 (Heil, Jr.), 4,953,564 (Berthelsen), and 5,496,360 (Hoffmann).

In certain of these prior art devices, molecular sieving materials are used to entrap the drug to be eluted in a cationic framework of aluminosilicates known as zeolites. This process involves first loading drug into cavities of such matrices in which the resident water molecules have been driven out by heating in a vacuum. Once loaded with drug and implanted, such a matrix will be exposed to the water of the tissue and will relinquish the entrapped drug molecules which are less polar than are the water molecules, thereby delivering the drug to the target tissue. *See,* Stokes, U.S. Patent Nos. 4,577,642, 4,711,251. However, once in contact with a water environment, such electrodes irreversibly deliver the entrapped drug.

In particular, the passive elution mechanisms of these prior art devices deliver the drug upon implantation without regard for amount or timing. Thus, once such a device is implanted, and the drug is automatically delivered to the insertion site tissue, no further delivery of drug is possible, and no physiologically-demanded dosage is possible.

In other prior art devices, a number of large-sized implanted apparatus have been described which can controllably release a drug into the body upon physiological demand. *See, e.g.*, U.S. Patent No. 4,003,379 (Ellinwood). Such devices are operated using complex pumps and valves, and require additional conduit tubing if the drug is to be delivered to a site distant from the reservoir/pump device. Thus, in the case of use of such a device to assist a cardiac stimulation electrode in the pacing or defibrillation of the heart, at least one additional conduit capable of delivering the drug to the heart or to the site of implantation of the lead is required over the lead itself. *See also*, U.S. Patent No. 5,220,917 (Cammilli).

In other prior art approaches, darts constructed out of biocompatible materials and which are part of an integrated stimulation electrode have been used to deliver a drug to target tissue. *See, e.g.*, U.S. Patent No. 5,531,780 (Vachon). In preferred embodiments, the dart includes a drug carried in a bioabsorbable, polymeric matrix. In this preferred embodiment, once the dart is projected into the target tissue, the embedded drug is slowly delivered to the target tissue by co-dissolution, diffusion, or resorption. The dart drug delivery mechanism is not under control of the stimulation device, being automatically and continuously delivered to the tissue upon fixation of the dart in the myocardium at the time of implant. It is also likely that the fixation of the dart itself will lead to increased inflammation, since active fixation of the dart in the tissue is required. In order to effect

release of the dart, mechanical moving parts must be integrated into the stimulation electrode.

Iontophoresis is a form of electrophoresis which uses an electrical potential or current in order to drive ionic species, such as ionic pharmaceuticals, toward a target treatment site. Iontophoresis can also include the concept of dragging non-ionic species toward a target site by incorporating the non-ionic drugs in an ionic solution or carrier. When water is the carrier material, electrophoretic movement of non-ionic species in that water to the target tissue is referred to as iontokinesis, or more specifically iontohydrokinesis.

Iontophoretic delivery of substances has been documented in the literature, as well. *See, e.g.*,: (1) Bange AK, Chien YW, "Hydrogel-based ionotherapeutic delivery devices for transdermal delivery of peptide 1 protein drugs," *Pharm. Res.* 10(5), 697-702, 1993; (2) Ferrendez-Ortiz A., Meyer BJ, Meilhec A., Felk E., Bodimon L., Fellon JT, Fuster V., Chesbro JH, Bediman JJ, "A New Approach for Local Intravascular Drug Delivery. Iontophoretic Balloon," *Circulation* 89(4), 1518-1522, 1994; and, (3) Singh S., Sing J., "Transdermal Drug Delivery by Passive Diffusion and Iontophoresis and a Review," Med. Res. Rev. 13(5), 569-621, 1993. Implantable iontophoretic drug delivery systems have also been previously described. *See, e.g.* R.W. Heil Jr., "Electrically Controllable, Non-Occluding, Body Implantable Drug Delivery System," U.S. Patent No. 5,041,107, issued August 20, 1991. *See also*, U.S. Patent No. 5,505,700 (Leone). These types of devices rely variously on iontophoresis, iontokinesis, and electroosmosis to deliver a drug or other molecule to a target tissue.

In such devices, the only purpose is to deliver a drug -- there is no dual capability to stimulate the surrounding tissue electrically. In particular, such devices cannot be used to simultaneously inject a drug into cardiac tissue while either pacing or defibrillating such tissue. Since there is no overt requirement to be conservative in use of power in these non-stimulatory devices, these references do not address means of power conservation coupled with controllable drug delivery.

Moreover, in each of such prior art devices relying on an electrophoretic process of one or another type, a separate catheter or other conduit is required to be inserted at or near the site of delivery of the drug molecule, over and above any other lead, catheter, or conduit which is used to otherwise stimulate the target tissue. Thus, where the prior art devices capable of iontophoretically delivering a drug to a cardiac tissue are to be used in combination with some sort of cardiac stimulation (pacing, defibrillation), separate drug delivery catheters and stimulation leads must be implanted.

No implantable, active-injection device capable of releasing a drug under the control of a pacemaker or automatic implantable cardioverter defibrillator ("AICD") has been disclosed in the prior art which utilizes the stimulation lead as the only conduit for drug to the target tissue. In

particular, no such stimulation lead utilizes an iontophoretic or iontokinetic mechanism to deliver drug to a cardiac tissue.

That which is needed and not provided by prior art devices or methods are implantable devices and methods of using them capable of delivering substance to a tissue, by iontophoretic processes through the stimulation lead itself, without need for additional conduits. Such devices and methods will preferably possess a reservoir of a deliverable substance that can be electrically and controllably delivered over extended periods of time without complex additional circuitry over that necessary for the stimulation device itself. More preferably, such devices and methods will operate using the existing electrodes and current sources of an implantable device, obviating the need for additional conduits, and will not cause such a drain on the current source as to require a larger current source or a more frequent replacement of the current source. Such devices will preferably not require valving, springs, or other such mechanical devices in order to effect drug-delivery. In particular, such devices and methods are needed for cardiac stimulation, where drugs may be provided to the cardiac tissue in order to reduce the threshold needed to pace or to defibrillate the heart.

Disclosure of the Invention

The present invention provides, for the first time, implantable stimulation devices and methods of using them, capable of delivering a substance to a tissue by an ion-dependent electrophoresis process. The devices and methods of the present invention provide a reservoir containing a substance which can be electrically delivered from the reservoir. These devices and methods operate using the existing electrodes and current sources of an implantable device, without need for an additional conduit or mechanical additions to the electrode, and without causing the modification or frequent exchange of the current source. In particular, the devices and methods of the invention are preferably cardiac pacemakers and defibrillators, in which drugs are provided to the cardiac tissue in order to reduce the threshold needed to pace or to defibrillate the heart. Most probably, the devices and methods of the invention are cardiac pacing electrodes capable of controllably delivering an anti-inflammatory drug.

In one aspect, the invention relates to an implantable stimulation lead capable of delivering a negatively-charged substance to a tissue. The lead comprises a cathodic reservoir capable of being loaded with the substance, a cathode electrode, and a source of current. The current source is connected electrically to the cathode electrode, which is in turn electrically connected to the reservoir. The electrical hook-up is done in such a manner as to allow electrophoretic displacement by the current of the charged substance from the reservoir into the tissue in which the lead is implanted.

While the preferred embodiments of the stimulation lead will utilize a positively-charged matrix

or reservoir, it is also possible to utilize a neutrally charged reservoir/matrix, so long as the entrapped drug is reasonably well maintained within the matrix/reservoir and can be electrically driven out of the matrix/reservoir by the repulsive force imparted by the net electrical current.

The reservoir matrix may also be coupled with a secondary reservoir in the stimulation lead. Thus, in certain embodiments, the stylet channel may function as the secondary reservoir. In pacing leads, this stylet channel may have a volume of 5 to 20 microliters. In defibrillation leads, the stylet channel which can function as a secondary reservoir will be much larger than 20 microliters.

The use of a neutral reservoir/matrix will be particularly useful where two or more drugs of varying charge or varying strength of charge are to be delivered. Thus, it is possible to load a neutral matrix with a mixture of a positively-charged drug and a negatively-charged drug. Depending upon the therapy required (i.e., anti-inflammatory positively-charged drug and anti-arrhythmic negatively-charged drug), the net current can be adjusted to either positive or negative, selectively delivering the drug of choice.

Net Current	Drug Delivered
+ Ve	A (positively-charged)
0	None
- Ve	B (negatively-charged)

Similarly, where two or more drugs of the same charge but of varying strength of charge are to be delivered, it is possible to vary the strength of the current to deliver more or less of the variably charged drugs;

Strength of Current	Drug Combination Preferentially Delivered
0	None
Mild	A
Strong	A + B
Very Strong	A + B + C

where the ionic strength of the drug is A < B < C.

Thus, it will be possible to coordinate the trapping energy (the energy which must be overcome by a current of a charge similar to the charge of the drug) and the selective release of a given drug. Where the trapping energy of drug A is less than that for drug B, if current is delivered below that energy level needed to dislodge drug A, no drug will be delivered. If the current is delivered above the level needed to dislodge drug A, but less than the level necessary to dislodge drug B, then only drug A will be released. If the current delivered is in excess of the trapping energy of drug B, then both drug A and B will be delivered.

In certain embodiments, the lead is a pacing lead. In other embodiments, the lead is a defibrillation lead. However, while the preferred modes of application relate to cardiac stimulation, similar modes of operation can be devised for muscular or neural stimulation.

The substance to be delivered by the leads of the invention will typically be a pharmaceutical. Thus, where it is desired to deliver an anti-inflammatory drug to the target tissue, the drug may be selected from drugs such as: glucocorticosteroids such as dexamethasone sodium phosphate, and other steroids, including fluoro-trihydroxy-methyl-pregnadiene/dione, and fluoro-methylprednisolone; ions and salts, such as sodium ion, sodium phosphate, the sodium salt of methoxy-methyl-naphthalene acetic acid, the sodium salt of isobutylphenyl-propionic acid. In a highly preferred embodiment, the delivered drug will be a salt of dexamethasone. Other anti-inflammatory drugs and substances which provide a desired therapeutic effect at the target tissue site of insertion can also be used so long as the substance can be delivered, either separately or in combination with a suitable coating, as an anion into the surrounding tissue. Because the devices of the invention allow for a controlled delivery of such drugs, more aggressive (more toxic) drugs can be utilized than would be safe where an implantable electrode is fitted with an uncontrolled drug-delivery system.

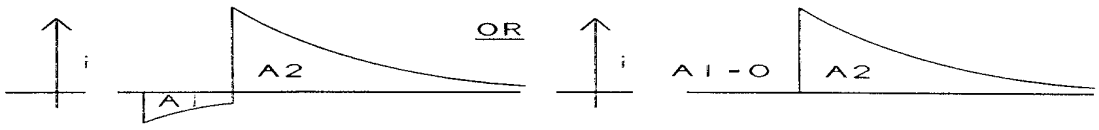
Other substances which will be usefully delivered using the electrode/drug-delivery systems of the invention will include antiarrhythmic and antifibrillation drugs. Such an antiarrhythmic drug is ibutelide. Other substances which may be delivered to target tissues will be thyroid hormones such as thyroxine, T3, their analogs, derivatives, and combinations thereof, for resuscitation of patients undergoing cardiac arrest. It is also possible to administer with the electrode of the invention, thrombolytic drugs, such as urokinase, streptokinase, and tissue plasminogen activator. It is also possible to deliver anionic gene therapy reagents such as nucleic acids.

Of course, combinations of such drugs may be impregnated into the matrix of the invention in certain embodiments. Thus, in particular embodiments it is possible to load the cathodic matrix with a relatively strongly-anionic drug as well as a relatively weakly-anionic drug. In such an embodiment, upon delivery of current from the anodic electrode to the cathodic matrix, the strongly-anionic drug can be made to preferentially electrophorese at a higher rate than the weakly-anionic drug. Whether used in combination or alone, the relative strength of the ionic nature of the drug can be used to regulate the dose/current ratio.

Where the lead of the invention is to deliver a neutrally- or positively-charged active ingredient which ingredient will, by itself, not be repulsed by the net negative current flow through the cathodic reservoir, it will be necessary to encapsulate or otherwise cause the neutral or positive substance to present a net negative charge to the current. This may be accomplished in a variety of ways

including solubilizing the neutral/cationic molecule in a negatively charged liposome, microcapsule or other covering. Thus, it will be possible to deliver neutral molecules non-soluble in aqueous solvents by emulsification with emulsifiers such as long chain fatty acids and lecithins. As the negatively-charged fatty acids are in iontophoretically transported out of the supporting matrix, they will carry the neutral drug with them. Similarly, with weakly-cationic drugs, it will be possible to bond them to bivalent anionic transport molecules. For instance, where the transport molecule has a weak acid site, the drug will form a weak salt upon delivery of the complexed transporter and drug to the tissue, and the weak salt will hydrolyze liberating the drug to the tissue.

While it will be preferred in most embodiments to utilize a negative current flow to displace negative ions from the reservoir for the power conservation reasons described herein, it is of course possible to displace positively-charged ions. This embodiment relies on an investment of energy over and above that utilized by a pacing pulse. Thus, waveforms resulting in such net positive current flow could be used, such as:



Such an embodiment may find particular usefulness in releasing anti-arrhythmic drugs.

The leads of the invention are those in which the net current is provided by truncation of an active discharge from a tank capacitor during a stimulation cycle. As will be seen in reference to the figures below, typical cardiac stimulation devices allow for an active discharge period following the stimulation pulse in order to bring the net electronic balance to zero. The leads of the invention extract variable amounts of the current from truncating such active discharging cycles and route it to the drug reservoir in order to displace drug therein. In most stimulation electrodes, the current is a net negative current flowing from the current source into the tissue through a cathode, which causes stimulation of the tissue and prevents corrosion of the electrode tip. For this reason, the preferred manner of operating the stimulation lead of the invention will involve displacement by a negative current.

Thus, in highly preferred embodiments, there is provided a cardiac pacing or defibrillation lead

capable of delivering a pharmaceutical such as an anti-inflammatory steroid to a cardiac tissue. The cathodic reservoir matrix is loaded with the steroid pre-implantation, and is in close electrical connection with an anodic electrode (cathode) and a source of current. The current is provided by truncating the active discharge from a tank capacitor of the pacemaker or AICD during the stimulation cycle allowing electrophoretic displacement of the steroid from the reservoir into the tissue.

The invention may also be viewed as a substantially improved device comprising a cathodic reservoir capable of being loaded with a pharmaceutical substance, an anodic electrode, and a source of current, each in electrical connection with the other, where the improvement comprises electrophoretic displacement by the current of the substance from the reservoir into the tissue, and where the current is provided by truncation of an active discharge from a DC DC blocking capacitor during a stimulation cycle.

The invention in other regards discloses methods of delivering a charged substance from an implantable stimulation electrode to a tissue. Such methods comprise filling a reservoir with the charged substance, placing an electrode in electrical connection via a body path with the reservoir, delivering a current of the same charge as that of the substance through the electrode and through the reservoir from a current source, thereby displacing the charged substance into the tissue.

The invention provides, in certain preferred embodiments, devices and methods by which a drug can be injected in the locality of an implanted cardiac stimulation electrode to lower the pacing or defibrillation threshold at the time of implant or at other times under the control of the implantable cardiac stimulator. For an AICD lowering the threshold just prior to shock permits smaller effective shocks, and thus, smaller batteries and capacitors. These smaller components, in turn, reduce the size of the AICD, decreasing trauma to the patient and its associated expenses or, alternatively, provide a mechanism to extend the life of the power supply.

The present invention substantially differs from prior art approaches using drug-elution electrodes, yet similarly lowers the thresholds for pacing and/or defibrillation. Moreover, the present invention in preferred embodiments allows the controlled release of a steroidal substance or other drug to selectively lower defibrillation thresholds prior to defibrillation, thus requiring less drug availability on the lead than with passive, drug-eluting electrodes. Moreover, more aggressive substances can be used, since their release occurs only when required to effectively lower pacing and/or defibrillation thresholds.

The active injection device of the invention is one that releases a drug in a controlled manner from an electrode, such as a stimulation electrode of a pacemaker or AICD system. The electrode does not elute a drug to lower the stimulation threshold, but rather forces it out on command from

the cardiac stimulation device.

In the present invention, whenever a condition arises which requires the cardiac stimulation device to lower the stimulation threshold, the controller of the implantable device causes a DC current flow or non-compensated pulse current flow between a combined iontophoresis/stimulating electrode and some other implanted reference electrode (e.g., the metallic enclosure of the implantable cardiac stimulation device). This current causes the release of a trapped drug from a reservoir matrix placed in electrical and physical contact with the stimulation electrode. The threshold-reducing drug then diffuses into the target tissue (e.g., myocardium) causing the reduction of inflammation, thrombosis or fibrosis.

In one possible embodiment, the output waveform of a cardiac stimulation device can be modified whenever iontophoretic drug delivery is desired. In the context of a pacemaker -- although the invention may be equally applied to AICDs and implantable neural or neuromuscular simulators -- the circuit can be made to deliver balanced or unbalanced stimulation under the control of the on-board microprocessor. Pulses which result in a balanced waveform -- one which produces zero net ionic current over the complete stimulation pulse cycle -- may stimulate the heart, but will not release the trapped drug. However, a charge imbalance with the correct polarity dominance will result in the active ejection of trapped drug from the reservoir matrix into the myocardium and adjacent tissues.

The matrix materials will preferably be physiologically inert and capable of retaining the charged drug to be delivered. Matrix materials which may be used include: polyacetic acid, polyglycolic acid, polyorthoesters, polyesters, polyurethanes, polyamino acids such as polylysine, lactic/glycolic acid copolymers, polyanhydrides and ion exchange resins such as sulfonated polytetrafluorethylene. Additionally, it is possible to construct the matrices from natural proteins or materials which are crosslinked using a crosslinking agent such as 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride. Such natural materials are those such as albumin, collagen, gelatin, keratin, potato starch hydrolyzed for use in electrophoresis, and agar-agar (agarose). Synthetic electrophoretic matrices are also suitable including polyacrylimide, acrylimide/bis-acrylimide mixtures, cellulose acetate, glyoxyl agarose, and SephadexTM (Pharmacia Fine Chemicals, Inc.) suitable for use in isoelectrofocusing. It is also possible to use combinations of such matrices, such as the combination of polyacrylimide and agarose, in order to fabricate the cathodic matrix of the invention.

In another embodiment, it is possible to fabricate multiple-layered cathodic reservoirs. Such multiple-layered reservoirs will find usefulness in certain embodiments in which there is desire to have additional control over the rate at which the charged substance is electrophoresed from the matrix. Thus, where it is desired to prevent diffusion of an anionic drug chiefly occurring at the

surface of the reservoir in contact with the target tissue, a relatively strongly-cationic matrix material may be used to cap a relatively weakly-cationic matrix material. This multiple-layered matrix embodiment may be preferentially utilized where a relatively more toxic, but more efficacious drug is to be initially utilized to lower the immediate post-implantation stimulation threshold, followed by a relatively less toxic, lower effectiveness drug. Similarly, where the target tissue may become refractory to the initial drug, a second drug delivered at a later time will assist in overcoming tissue non-responsiveness.

Additionally, a multiple-layered matrix approach will find usefulness where drugs are to be administered temporally for different therapies. Thus, in most instances, a first drug will be usefully delivered to the target tissue in order to lower the immediately post-implantation stimulation threshold. However, and particularly in patients with a history of cardiac arrhythmia or fibrillation, it may be useful to charge a second layer with an anti-arrhythmic or antifibrillation drug, which drug is delivered only upon the necessary physiological demand. Similar combinations may be made in patients with histories of cardiac arrest, where thyroid hormone therapy may be desired.

When a multiple-layered matrix is used, it is also possible to sequentially deliver a gradually declining (or increasing, or cyclical) concentration of a drug. In such an embodiment, the distal most matrix reservoir may contain a first lower dose of a drug, followed by a next most distal matrix with a concentration of drug higher than the first, and so on.

Of course, because the stimulation leads of the present invention are under the control of software in the implanted device, it will be possible to program a variety of drug-delivery protocols. Such software will be particularly valuable where the drug regimen involves multi-drug delivery.

A distinct advantage that the present invention has over prior art approaches requiring water-soluble drugs as a component of the drug-delivery system, is that water-insoluble substances may be impregnated into the matrix and delivered by iontophoretic means to the target tissue without need for solubilization in aqueous media, such as by raising or lowering the pH, or adding solubilizing agents. Thus, where an anti-inflammatory agent such as the sodium salt of methoxy-methyl-naphthalene acetic acid is to be used, which substance is not soluble in aqueous media in its acid form, the insoluble form of the drug may be incorporated into a suitable matrix, either with or without a coating, and delivered to the target tissue. Similarly, because there is no requirement that the charged substances be solubilized while entrapped in the cathodic reservoir, it is possible to impregnate the matrix with highly-concentrated crystalline forms of certain substances such as anti-inflammatory drugs, especially where such drugs are loaded as the salt of an acid or base of the active drug ionic species.

In another embodiment of the invention, it is possible to attach an auxiliary reservoir in fluid connection to the cathodic matrix reservoir in order to provide a reserve of additional drug useful in recharging the cathodic matrix as drug is eluted into the target tissue. In such an embodiment, the auxiliary reservoir is attached to the cathodic matrix which is in turn in contact with the target tissue. As drug is iontophoretically eluted into the target tissue, replacement drug is osmotically drawn from the auxiliary reservoir to take its place. Of course, the auxiliary reservoir may contain an identical drug as that initially impregnated into the cathodic matrix pre-implantation, or it may contain a drug distinct from that initially loaded in the matrix. Similarly to the multiple-layered matrix embodiment above, this embodiment may be preferentially utilized where a relatively more toxic, but more efficacious drug is to be initially utilized to lower the immediate post-implantation stimulation threshold, followed by a relatively less toxic, lower effectiveness drug.

Delivery of the charged substance or delivery of the substance in its charged carrier is carried out iontophoretically. In this manner, the substance such as a drug or its carrier having a charge of the same polarity as that of the electrode is forced to migrate away from the matrix reservoir. Precise control can be maintained over the dosage of the delivered drug in that the amount delivered to the target tissue is directly proportional to the product of the current flow and time (Faraday's Law of Electrolysis).

It is also possible to separate the cathodic reservoir containing the drug from direct contact with the target tissue by interposing a permeable membrane. Such membranes can be constructed out of ion exchange membrane materials such as known to those of skill in the art. See U.S. Patent 5,385,579 (Helland): Wiegand et al. *PACE* 19:1155-1161 (1996). One such membrane will be cellophane.

Control of the delivery of the drug by the devices of the invention is variable. It is possible to merely program the device to deliver its entire load of iontophoretically deliverable drug upon implantation or shortly thereafter. In this mode of operation, the devices of the invention operate like prior art devices, albeit utilizing the novel delivery mechanisms of the invention. More preferably, the devices of the invention are programmed to monitor one or more physiological conditions in order to coincide the timing of the drug delivery to the greatest physiological demand.

Thus, where the physiological criterion monitored by the device is the stimulation threshold of the target tissue, drug delivery occurs only when such threshold reaches a predetermined maximum. Where the physiological parameter monitored by the devices of the invention is arrhythmia or fibrillation, drug delivery is coincident with detection of such conditions.

Brief Description of the Drawings

Fig. 1 depicts the drug-delivering stimulation electrode in electrical connection with the

iontophoretic and stimulating circuit.

Fig. 2 is a sectional view of the drug-delivering electrode in electrical connection with the iontophoretic circuit which is in turn electrically connected to the current source, wherein in the absence of current flow by virtue of the switched off circuit, no iontophoresis of the matrix-entrapped particles occurs.

Fig. 3 is a sectional view of the drug-delivering electrode in electrical connection with the iontophoretic circuit which is in turn electrically connected to the current source, wherein in the initial stages of current flow by virtue of the switched on circuit, iontophoresis of the matrix-entrapped particles into the surrounding tissue is beginning to occur.

Fig. 4 is a sectional view of the drug-delivering electrode in electrical connection with the iontophoretic circuit which is in turn electrically connected to the current source, wherein in the later stages of current flow by virtue of the switched on circuit, iontophoresis of the matrix-entrapped particles into the surrounding tissue is complete.

Fig. 5 is a diagram of the switching cycles and the resultant waveform of the current over time, wherein by virtue of the closing of switch S3 throughout the active discharge period, the pacing pulse current is balanced and no excess current is delivered to the cathodic drug reservoir.

Fig. 6 is a diagram of the switching cycles and the resultant waveform of the current over time, wherein by virtue of the premature opening of switch S3 and closure of switch S4 prior to the end of the normal active discharge period, a portion of the excess current is delivered to the cathodic drug reservoir.

Fig. 7 is a diagram of the switching cycles and the resultant waveform of the current over time, wherein by virtue of the failure to close switch S3 at any time and by shunting the DC-blocking capacitor through switch S4, all excess current is delivered to the cathodic drug reservoir.

Best Mode for Carrying Out the Invention

Turning now to the figures, exemplary devices of the invention are seen. For purposes of example, operation of preferred modes using the devices of the invention are described in a cardiac pacing application. Of course, it will be understood by those of skill in the art that similar examples could be given for use of the devices of the invention for different cardiac stimulation scenarios, particularly for AICD or defibrillation applications. Similarly, while the preferred modes of application each relate to cardiac stimulation, similar modes of operation can be devised for other muscles or for neural stimulation. Additionally, where the ability of the leads to simultaneously electrophorese ionic species with the ability of the leads to deliver a charge to a tissue can be usefully applied, such embodiments are expressly included herein. For instance, it will be possible to electrophorese nucleic acids encoding genetic information into the cells of a target tissue. This

embodiment will be especially useful in those instances in which only a transient expression of the transgene is desired and that expression is to be carried out over extended time frames. For example, in the treatment of certain types of tumors, it may be desirable to electrically deliver a transiently-expressed gene encoding a toxin in order to kill metabolically active tumor cells.

Generally, then, in a pacing application as shown in Fig. 1 and Fig. 2, during a pacing pulse, throughout which drug 18 should not be released from matrix 22 comprising electrode tip 14, the charge derived from current source 16 housed within can 24 as formed by capacitor 28 which is charged by voltage source 30, is discharged across interconnection 20 on lead 12 for a given time into myocardium 26 through electrode 10 to cause stimulation. The circuit is completed by way of switch S2, through the lead system 12 and DC-blocking capacitor 34. The charge accumulated into DC-blocking capacitor 34 is then completely discharged by way of switch S3 and resistor 32 into myocardium 26, thus generating a reverse current flow, resulting in the complete balancing of the charge released during the stimulation phase. The system is grounded at ground 36 by interconnections 38, 40, 42 and 44.

If the discharge of DC-blocking capacitor 34 is prematurely terminated however, less than complete balancing occurs, and a dose of drug 18 is actively ejected from matrix reservoir 22. The magnitude of the dose is proportional to the charge imbalance. This premature termination is achieved by short-circuiting DC-blocking capacitor 34 at the time of desired premature termination. Maximum drug release per pacing pulse is achieved by bypassing completely DC-blocking capacitor 34 while discharging tank capacitor 28 into lead system 12 and myocardium 26.

In one possible embodiment, as shown in Fig. 5, the standard current output waveform A1A2 of a pulse generator can be modified whenever iontophoretic drug delivery is desired. As shown in Figures 5-7, A1 and A2 are the areas between the current curve and the baseline. The ratios of these areas are proportional to the charge delivered. In the context of a pacemaker -- although the invention can be equally applied to AICDs, implantable neural or neuromuscular simulators and cardiomyoplasty simulators as well as other uses described herein -- the circuit can be made to deliver balanced or unbalanced stimulation under the control of an on-board microprocessor. Pulses which result in a balanced waveform -- one which produces zero net ionic current (A1 = A2) -- may stimulate the heart, but not release trapped anti-inflammatory drugs. However, charge imbalance with the correct charge polarity dominance will result in the active ejection of trapped drug from the reservoir matrix into the myocardium.

During a pacing pulse when the drug should not be released, tank capacitor 28 (Fig. 1) is charged by source 30 through switch S1. It is then discharged through lead system 12 (Fig. 1) into the myocardium by way of switch S2 and DC-blocking capacitor 34. The charge accumulated into

DC-blocking capacitor 34 is then discharged through lead system 12 into myocardium 26 by closing switch S3. As shown in Fig. 5, the complete discharge of DC -blocking capacitor 34 balances the charge released during the stimulation phase.

Referring now to Fig. 4 and Fig. 6, if the active discharge of DC blocking capacitor 34 is prematurely terminated, however, less than balancing occurs, and a dose of drug 18 is actively ejected from matrix reservoir 22. The magnitude of the dose is proportional to the charge imbalance. This premature termination is achieved by prematurely opening switch S3, while closing switch S4 at t2.

Maximum drug release per pulse, as shown in Fig. 4 and Fig. 7, is achieved by bypassing DC blocking capacitor 34 while discharging tank capacitor 28 into lead system 12 and myocardium 26.

WHAT IS CLAIMED IS:

1. An implantable stimulation lead capable of actively and controllably injecting a charged substance into a tissue, comprising:

a reservoir of opposite charge to that of said substance capable of being loaded with and retaining said substance;

an electrode of a similar charge to that of said substance; and,

a source of current;

each in electrical connection with the other in a manner allowing electrophoretic displacement by said current of said substance from said reservoir into said tissue.

2. The lead of claim 1, wherein said substance is negatively-charge.

3. The lead of claim 1, wherein said substance is positively-charged.

4. The lead of any of the foregoing claims, wherein said lead is a pacing lead.

5. The lead of any of claims 1, 2 or 3, wherein said lead is a defibrillation lead.

6. The lead of any of the foregoing claims, wherein said substance is a pharmaceutical.

7. The lead of claim 6, wherein said pharmaceutical is an anti-inflammatory pharmaceutical.

8. The lead of claim 7, wherein said anti-inflammatory is a steroid.

9. The lead of claim 6, wherein said pharmaceutical is an antibiotic.

10. The lead of claim 6, wherein said pharmaceutical is an anti-arrhythmic pharmaceutical.

11. The lead of claim 1, wherein said substance encapsulates a positively-charged active ingredient.

12. The lead of claim 11, wherein said active ingredient is a pharmaceutical.

13. The lead of any of the foregoing claims, wherein said current is provided by truncation of an active discharge from a capacitor during a stimulation cycle.

14. A cardiac pacing lead capable of actively and controllably injecting a pharmaceutical into a cardiac tissue, comprising:

a reservoir matrix of a charge opposite to that of said pharmaceutical capable of being loaded with and retaining said pharmaceutical;

an electrode of a charge similar to that of said pharmaceutical; and,

a source of current, wherein said current is provided by truncation of an active discharge from a capacitor during a stimulation cycle;

each in electrical connection with the other in a manner allowing electrophoretic displacement of said pharmaceutical from said reservoir into said tissue.

15. A cardiac defibrillation lead capable of actively and controllably injecting a charged pharmaceutical into a cardiac tissue, comprising:

a reservoir matrix of a charge opposite to that of said pharmaceutical capable of being

loaded with and retaining said pharmaceutical;

an electrode of a charge similar to that of said pharmaceutical; and,

a source of current, wherein said current is provided by truncation of an active discharge from a capacitor during a stimulation cycle;

each in electrical connection with the other in a manner allowing electrophoretic displacement by said current of said pharmaceutical from said reservoir into said tissue.

16. An improved stimulation lead capable of delivering a negatively-charged substance to a tissue, comprising a cathodic reservoir capable of being loaded with said substance, an anodic electrode, and a source of current, each in electrical connection with the other, wherein the improvement comprises:

electrophoretic displacement by said current of said substance from said reservoir into said tissue, wherein said current is provided by truncation of an active discharge from a capacitor during a stimulation cycle.

FIG. 1

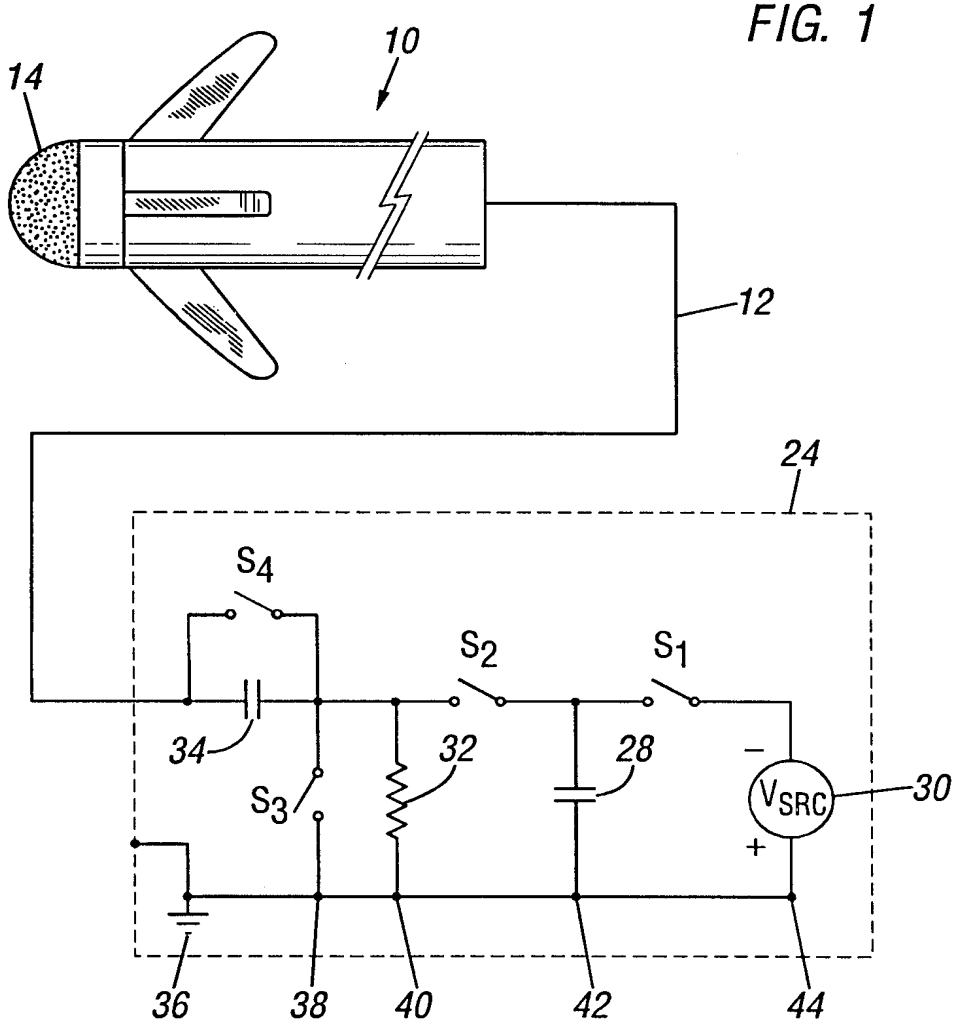

14
10
12
24
S4
S2
S1
34
32
28
S3
VSRC
30
36
38
40
42
44

FIG. 2

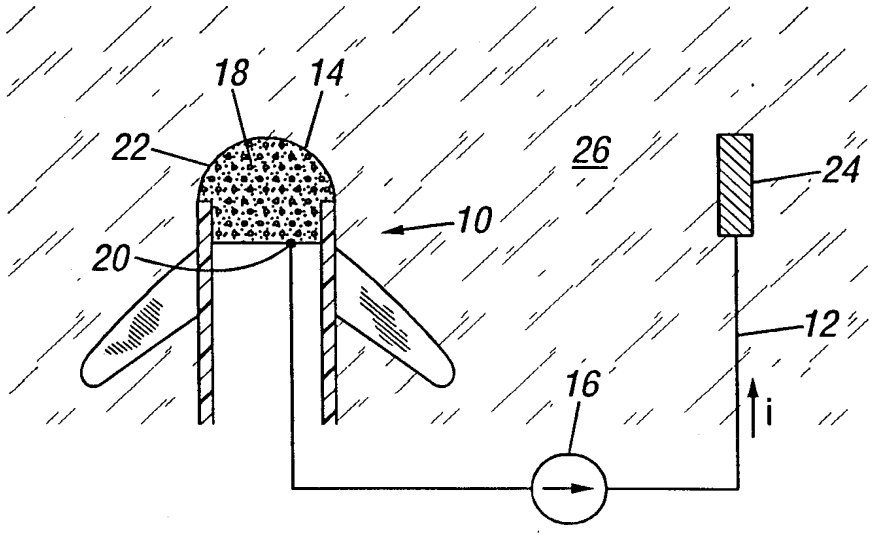

18
14
22
26
24
10
20
12
16
i

FIG. 3

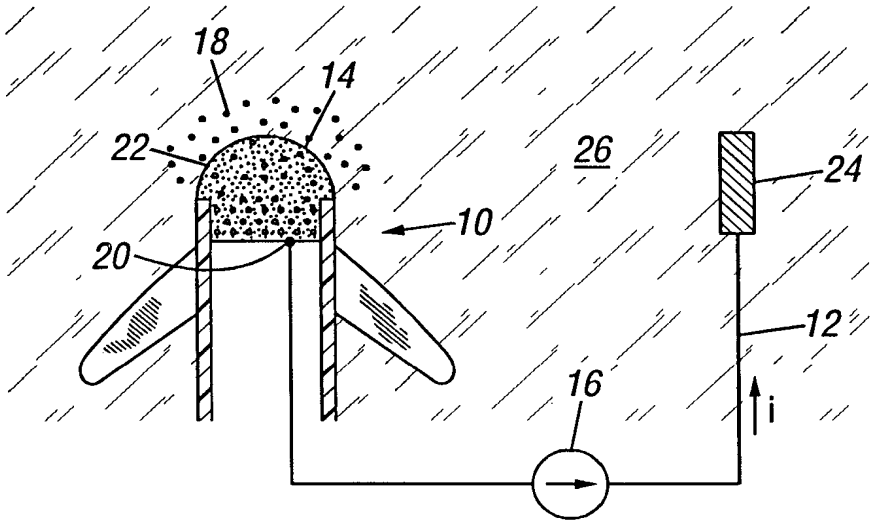


FIG. 4

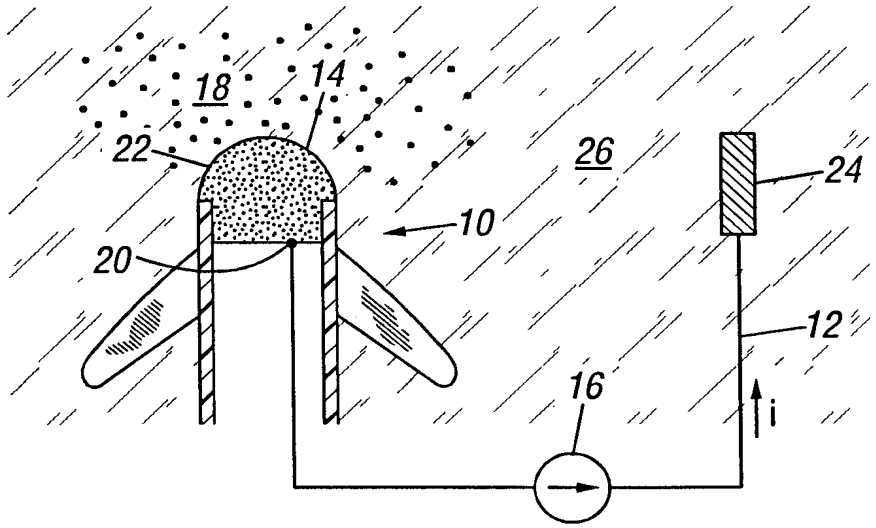


FIG. 5

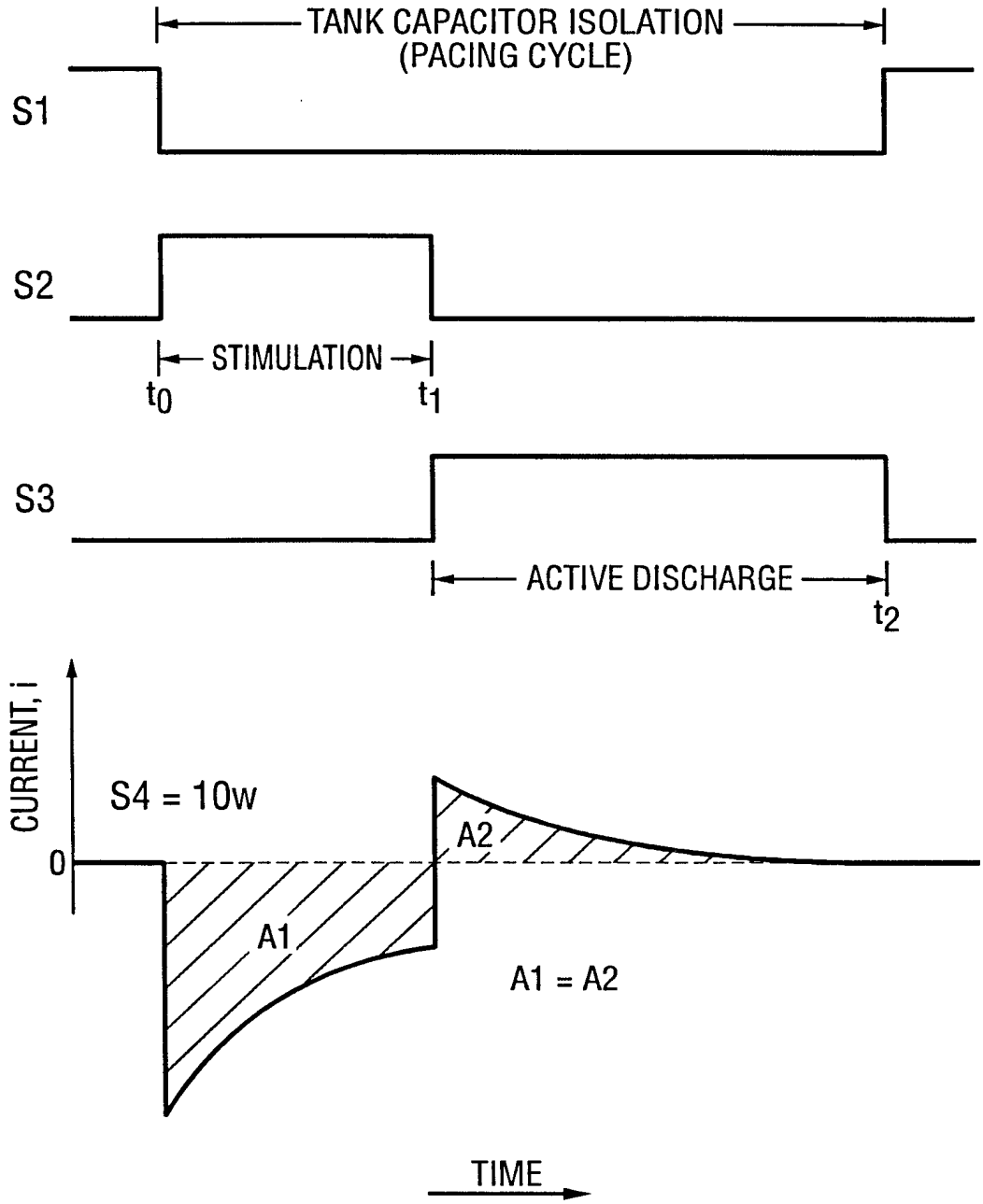

TANK CAPACITOR ISOLATION
(PACING CYCLE)
S1
S2
STIMULATION
t_0
t_1
S3
ACTIVE DISCHARGE
t_2
CURRENT, i
S4 = 10w
0
A2
A1
A1 = A2
TIME

FIG. 6

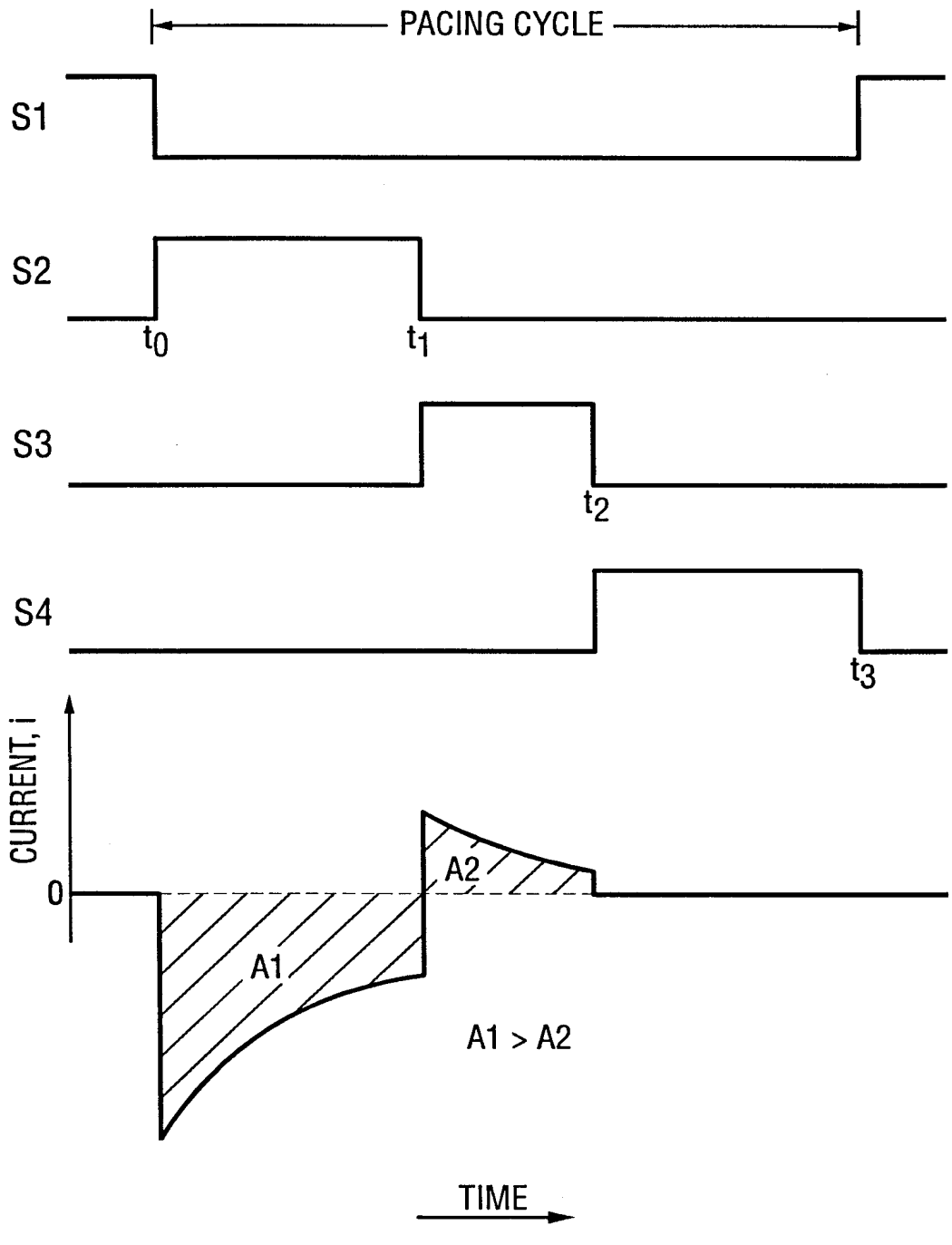
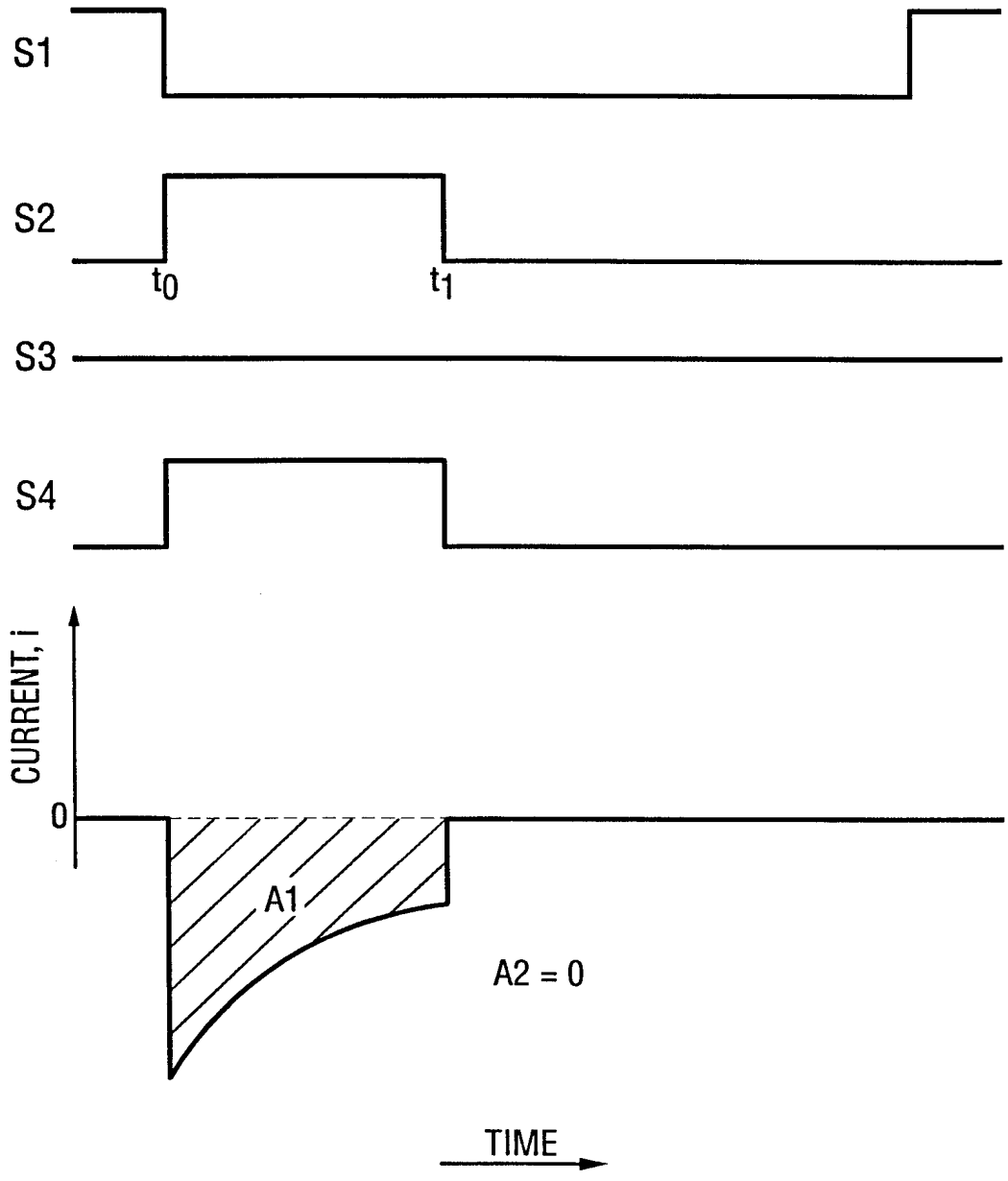


FIG. 7



INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/US 97/15734

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/05 A61N1/362

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 505 700 A (LEONE JAMES E ET AL) 9 April 1996 cited in the application see page 3, line 66 - page 7, line 65; figures	1,4-6, 10,14-16
A	US 4 003 379 A (ELLINWOOD JR EVERETT H) 18 January 1977 cited in the application see column 3, line 48 - column 18, line 46; figures	1,4-6, 10,14-16
A	US 4 456 012 A (LATTIN GARY A) 26 June 1984 see column 3, line 10 - column 8, line 23; figures	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1998	05/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rakotondrajaona, C

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INTERNATIONAL SEARCH REPORT

Inte ..ional Application No
PCT/US 97/15734

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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1

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